Simple Synthesis of Novel 1',4'-Dimethyl Branched Carbovir Analogues

Aihong Kim and Joon Hee Hong*

*College of Pharmacy, Chosun University, Gwangju 501-759, Korea. *E-mail: hongjh@chosun.ac.kr*

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Novel 1',4'-dimethyl branched carbocyclic nucleosides were synthesized from acetol. The 4'-methyl group was installed *via* a Claisen rearrangement reaction, and the carbonyl addition of methylmagnesium bromide was used to introduce the 1'-methyl group. The coupling of nucleosidic bases and desilylation was used to produce a series of novel nucleosides.

Key Words : Antiviral agents, Branched nucleoside, Carbocyclic nucleoside

Introduction

The replacement of the oxygen atom on the furanose ring by carbon is of particular interest because the resulting carbocyclic nucleosides[1] have a greater metabolic stability to phosphorylase[2] which cleaves the glycosidic bond of nucleosides. Many carbocyclic nucleosides have interesting biological activities, particularly in the areas of antiviral and anticancer chemotherapy, because the cyclopentane ring of these compounds can imitate the furanose moiety. The recent discovery of olefinic carbocyclic nucleosides, such as carbovir (**1**)[3] and abacavir (**2**),[4] which are potential anti-HIV agents, have increased interests in the search for novel nucleosides in this class of compounds. However, the side effects[5] with these antiviral agents as well as the emergence of drug-resistant mutants are a continuing problem.[6] Therefore, the judicious combination chemotherapy is the optimum way of improving the quality of life and survival of patients infected with the HIV-1 virus.

Recently, several branched nucleosides were synthesized and found to be potent antitumor or antiviral agents. Among them, 4'(α)-*C*-hydroxymethyl thymidine (**3**),[7] which has additional branch at the 4'-position, was reported to have potent antiviral activity (Figure 1).

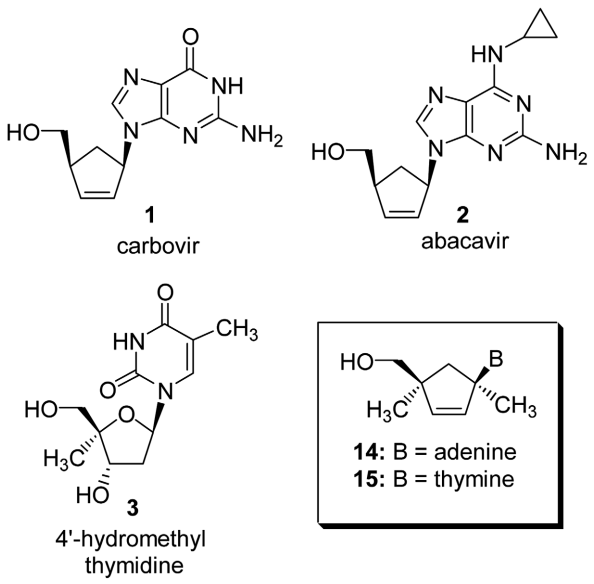


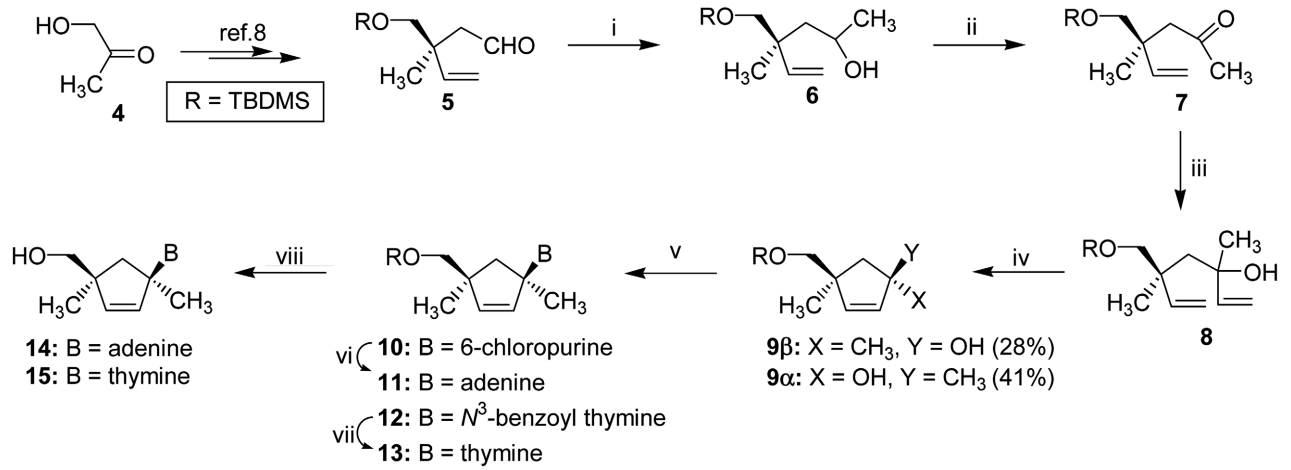
Figure 1. Synthesis rationale of the target nucleosides.

In view of the stimulating results of olefinic nucleosides and as part of an ongoing investigation into the discovery of less toxic and more effective antiviral agents, we synthesized 1',4'-dimethyl branched carbocyclic nucleosides.

Results and Discussion

As shown in Scheme 1, aldehyde **5**, which is readily synthesized from acetol Claisen rearrangement using a previously reported method,[8] was subjected to the carbonyl addition of CH_3MgBr to give compound **6** as a diastereomeric mixture. Without separation, the alcohol derivative **6** was oxidized using PCC to give a single compound **7**. The ketone **7** was subjected to Grignard addition using vinylmagnesium bromide to give a divinyl **8** as an inseparable diastereomeric mixture. The bis-olefin **8** was cyclized under ring-closing metathesis conditions using a second-generation Grubbs' catalyst [(Im)$Cl_2PCy_3RuCHPh$][9] to afford the cyclopentenols **9**α and **9**β, respectively. The stereochemical assignments were based on the NOE experiments. Upon the irradiation of C_1-CH_3, a strong NOE was observed at the methylene protons of the hydroxymethyl group of compound **9**α, but not at the methylene protons of **9**β (Figure 2).

The Mitsunobu reactions were used to couple the cyclopentenol with the nucleosidic bases.[10] This methodology has been successfully used to synthesize the target nucleosides with the desired β-configuration. The required β-configurations of nucleosides **10** and **12** were successfully controlled from the α-configuration of compound **9**α. The success of the Mitsunobu reactions in the synthesis of the nucleoside analogues depends on the conditions. The appropriate choice of solvent system, temperature and procedure are essential for the regioselectivity as well as for the yield. In purine synthesis, a 2 : 1 mixture of dioxane and DMF were used as the solvent for the coupling of the cyclopentenol **9**α with 6-chloropurine instead of THF. The heterocyclic bases had a better solubility in the dioxane-DMF mixture resulting in better yields. The slow addition of diisopropylazodicarboxylate (DIAD) to a mixture of cyclo-



Scheme 1. Synthesis of 1',4'-dimethyl branched nucleosides. Reagents: i) CH_3MgBr, THF; ii) PCC, 4A-MS, CH_2Cl_2; iii) CH_2=CHMgBr, THF; iv) Grubbs' catalyst (II), CH_2Cl_2; v) nucleosidic bases, DIAD, PPh_3, dioxane/DMF; vi) NH_3/MeOH, steel bomb; vii) NaOMe, MeOH; viii) TBAF, THF.

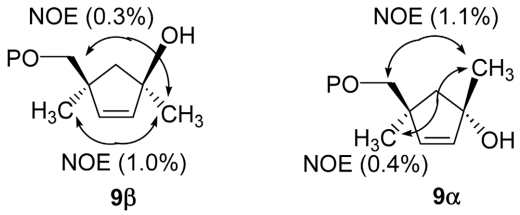


Figure 2. NOE results of compound **9**α and **9**β.

pentenol **9**α, triphenylphosphine and the corresponding purine base in an anhydrous solvent gave a yellow solution, which was then stirred for 2 hours at –20 °C to give the protected 6-Cl-purine analogue **10**. The 6-chloropurine **10** was converted to a protected adenosine analogue **11** by treating it with a saturated solution of metahnolic ammonia in a steel bomb at 90-95 °C overnight.

On the other hand, the synthesis of the pyrimidine nucleosides was more complex than in the case of purine due to the formation of O^2-alkylated by-products. The formation of these compounds was inevitable under the conditions used. However, the ratio of *N*- to *O*-alkylation was improved by changing the solvent to a 2 : 1 mixture of dioxane-DMF. The regioisomer of the O^2-alkylated compounds were easily confirmed by a comparison of the published UV spectra.[11] The condensation of compound **9**α with N^3-benzoyl thymine under the similar Mitsunobu conditions gave the protected thymine analogue **12**, which was debenzoylated with sodium methoxide to afford the corresponding nucleoside **13**. The final nucleosides **14** and **15** were obtained from the corresponding protected nucleosides by treating them with tetrabutylammonium fluoride (TBAF). Based on an extensive literature search, compounds **14** and **15** appear to be novel nucleosides. Antiviral activity assays were performed using the synthesized nucleosides against HIV-1, HSV-1, HSV-2 and HCMV. However, these compounds showed no significant activity or cytotoxicity at concentrations up to 100 μM.

In summary, a concise synthetic method for synthesizing 1',4'-dimethyl branched carbocyclic nucleosides from a α-hydroxy ketone was developed. Based on this strategy, the enantiomeric synthesis of a doubly branched nucleoside with different bases and substituents is currently underway.

Experimentals and Methods

The melting points were determined on a Mel-tem II laboratory device and were uncorrected. The NMR spectra were recorded on a JEOL JNM-LA 300 spectrometer. The chemical shifts are reported as parts per million (δ), and the signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). The UV spectra were obtained using a Beckman DU-7 spectrophotometer. The elemental analyses were performed using an Elemental Analyzer System (EA 1112). TLC was performed on Uniplates (silica gel) that were purchased from Analtech Co. Unless otherwise specified, all the reactions were carried out in a N_2 atmosphere. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. The dry THF was obtained by distillation from Na and benzophenone immediately before use.

(±)-4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methylhex-5-en-2-ol (6): To a solution of compound **5** (2.57 g, 10.6 mmol) in dry THF (80 mL), methyl magnesium bromide (12.7 mL, 1.0 M solution in THF) was added slowly at −78 °C. After 4 h, a saturated NH_4Cl solution (7 mL) was added, and the reaction mixture was warmed slowly to room temperature. The mixture was extracted with EtOAc (300 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and then evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 20) to give compound **6** (2.19 g, 80%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ5.98-5.58 (m, 1H), 5.72-5.61 (m, 1H), 5.05-4.90 (m, 4H), 3.90 (m, 1H), 3.88 (m, 3H), 3.46-3.31 (m, 5H), 1.58-1.38 (m, 4H), 1.08 (s, 3H), 0.97 (s, 3H), 0.83 (s, 18H), 0.23 (s, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 145.63, 144.05, 113.32,

112.13, 71.03, 70.56, 64.40, 63.81, 48.74, 41.33, 41.14, 25.81, 24.51, 22.74, 20.61, 18.29, –5.54.

(±)-4-(*tert*-Butyldimethylsilanyloxymethyl)-4-methylhex-5-en-2-one (7): To a solution of compound **6** (827 mg, 3.2 mmol) in CH_2Cl_2 (50 mL), 4 Å molecular sieves (1.8 g) and PCC (1.72 g, 8.0 mmol) were added slowly at 0 °C, and stirred for 6 h at room temperature. To the resulting mixture, excess diethyl ether (300 mL) was then added. The mixture was stirred vigorously for 3 h at the same temperature, and the resulting solid was filtered through a short silica gel column. The filtrate was concentrated under vacuum, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 40) to give compound **7** (730 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.95 (dd, J = 17.7, 11.1 Hz, 1H), 5.04 (d, J = 10.5 Hz, 1H), 4.95 (d, J = 16.2 Hz, 1H), 3.46 (d, J = 8.8 Hz, 1H), 3.37 (d, J = 8.8 Hz, 1H), 2.51 (d, J = 14.7 Hz, 1H), 2.43 (d, J = 8.7 Hz, 1H), 2.09 (s, 3H), 1.05 (s, 3H), 0.86 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.43, 143.57, 112.95, 69.90, 49.75, 41.58, 32.11, 25.84, 20.79, 18.26, -5.56; Anal calc for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.71; H, 11.12.

(±)-5-(*tert*-Butyldimethylsilanyloxymethyl)-3,5-dimethylhepta-1,6-dien-3-ol (8): To a solution of compound **7** (1.49 g, 5.84 mmol) in dry THF (80 mL), vinyl magnesium bromide (7.00 mL, 1.0 M solution in THF) was added slowly at −78 °C. After 3 h, a saturated NH_4Cl solution (6 mL) was then added, and the reaction mixture was warmed slowly to room temperature and extracted with EtOAc (300 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 30) to give compound **8** (1.19 g, 72%) as a diastereomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02-5.84 (m, 2H), 4.96-4.22 (m, 4H), 3.51-3.28 (m, 2H), 1.80-1.61 (m, 2H), 1.16 (s, 3H), 0.97 (s, 3H), 0.81 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 146.83, 146.10, 145.12, 112.50, 111.91, 110.27, 73.20, 72.87, 71.09, 70.21, 51.38, 50.81, 42.11, 31.57, 31.32, 25.87, 23.56, 23.19, 18.35, –5.52.

(*rel*)-(1*S*,4*S*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-1,4-dimethylcyclopent-2-enol (9α) and (*rel*)-(1*R*,4*S*)-4-(*tert*-butyldimethylsilanyloxymethyl)-1,4-dimethylcyclopent-2-enol (9β): To a solution of compound **8** (705 mg, 2.48 mmol) in dry CH_2Cl_2 (20 mL), a second generation Grubbs' catalyst (12.5 mg, 0.015 mmol) was added. The reaction mixture was reflux overnight, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 30) to give the cyclopentenols **9**α (260 mg, 41%) and **9**β (178 mg, 28%): compound **9**α: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.66 (d, J = 5.1 Hz, 1H), 5.29 (d, J = 5.4 Hz, 1H), 3.33 (dd, J = 11.7, 9.6 Hz, 2H), 1.87 (d, J = 14.1 Hz, 1H), 1.63 (d, J = 14.2 Hz, 1H), 1.31 (s, 3H), 0.93 (s, 3H), 0.81 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.61, 137.84, 81.55, 69.95, 51.37, 50.53, 26.37, 26.04, 23.71, 18.61, −5.52; compound **9**β: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (s, 2H), 3.34 (dd, J = 15.6, 9.3 Hz, 2H), 1.99 (d, J = 18.8 Hz, 1H), 1.64 (d, J = 14.1 Hz, 1H), 1.37 (s, 3H), 1.11 (s, 3H), 0.86 (s, 9H), 0.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.09, 136.50, 83.55, 70.70, 51.37, 51.06, 49.78, 28.75, 25.89, 25.17, 18.31, -5.46.

(*rel*)-(1′*R*,4′*S*)-9-[4-(*tert*-Butyldimethylsilanyloxymethyl)-1,4-dimethylcyclopent-2-enyl]-6-chloropurine (10): To a solution containing compound **9**α (230.8 mg, 0.9 mmol), triphenylphosphine (1.41 g, 2.7 mmol) and 6-chloropurine (347 mg, 2.24 mmol) in anhydrous dioxane (7 mL) and DMF (5 mL), diisopropyl azodicarboxylate (0.49 mL) was added dropwise at –20 °C for 30 min. under nitrogen. The reaction mixture was stirred for 2 h at –20 °C under nitrogen. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1 : 3) to give compound **10** (109 mg, 31%): UV (MeOH) λ_{max} 266.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.11 (s, 1H), 5.74 (d, J = 5.2 Hz, 1H), 5.41 (d, J = 5.4 Hz, 1H), 3.56 (dd, J = 12.0, 9.2 Hz, 2H), 1.82 (d, J = 13.6 Hz, 1H), 1.62 (d, J = 12.8 Hz, 1H), 1.34 (s, 3H), 0.99 (s, 3H), 0.87 (s, 9H), 0.1 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.45, 151.12, 149.45, 143.45, 141.81, 137.45, 136.42, 69.23, 62.76, 52.81, 49.71, 26.76, 25.82, 23.66, 18.43, –5.57.

(*rel*)-(1′*R*,4′*S*)-9-[4-(*tert*-Butyldimethylsilanyloxymethyl)-1,4-dimethylcyclopent-2-enyl]-adenine (11): Compound **10** (102 mg, 0.26 mmol) was dissolved in saturated methanolic ammonia (15 mL) and the resulting solution was stirred overnight at 90-95 °C in a steel bomb. After removing the reaction solvent, the residue was purified by silica gel column chromatography (EtOAc/hexane/MeOH, 1 : 3 : 0.3) to give compound **11** (72.8 mg, 75%) as a solid: UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (s, 1H), 7.94 (s, 1H), 5.79 (d, J = 5.4 Hz, 1H), 5.44 (d, J = 5.2 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.42 (d, J = 11.0 Hz, 1H), 1.87 (d, J = 12.2 Hz, 1H), 1.71 (d, J = 11.8 Hz, 1H), 1.36 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.2 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.34, 152.77, 150.56, 141.72, 137.56, 136.23, 119.31, 68.56, 60.92, 52.72, 50.76, 26.56, 25.76, 23.71, 18.56, –5.56.

(*rel*)-(1′*R*,4′*S*)-1-[4-(*tert*-Butyldimethylsilanyloxymethyl)-1,4-dimethylcyclopent-2-enyl]-N^3-benzoyl thymine (12): Compound **12** was synthesized from compound **9** and N^3-benzoyl thymine using the method described for synthesizing compound **10**: yield 35%; UV (MeOH) λ_{max} 254.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88-7.41 (m, 6H), 5.89 (d, J = 5.2 Hz, 1H), 5.65 (d, J = 5.4 Hz, 1H), 3.50 (dd, J = 11.8, 8.8 Hz, 2H), 1.90 (d, J = 12.2 Hz, 1H), 1.73 (d, J = 12.4 Hz, 1H), 1.40 (s, 3H), 1.26 (s, 3H), 0.98 (s, 3H), 0.85 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.76, 163.31, 151.23, 138.84, 137.74, 134.65, 130.33, 107.34, 69.67, 62.23, 53.65, 48.32, 26.54, 25.61, 23.81, 18.59, 12.14, –5.43.

(*rel*)-(1′*R*,4′*S*)-1-[4-(*tert*-Butyldimethylsilanyloxymethyl)-1,4-dimethylcyclopent-2-enyl]-thymine (13): To a stirred solution of compound **12** (94 mg, 0.2 mmol) in MeOH (5 mL), NaOMe (0.3 mL, 1 M solution in MeOH) was added at 0 °C under nitrogen and stirred overnight. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure. The residue was purified by silica

gel column chromatography (EtOAc/Hexane/MeOH, 2 : 1 : 0.3) to give the compound **13** (151 mg, 70%) as a solid: UV (MeOH) λ_{max} 268.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (br s, 1H), 7.31 (s, 1H), 5.90 (d, J = 5.8 Hz, 1H), 5.61 (d, J = 6.0 Hz, 1H), 3.56 (d, J = 9.6 Hz, 1H), 3.42 (d, J = 9.8 Hz, 2H), 1.92 (d, J = 9.2 Hz, 1H), 1.74 (d, J = 10.4 Hz, 1H), 1.78 (s, 3H), 1.45 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.07, 151.72, 142.56, 108.55, 67.54, 60.32, 51.87, 47.32, 26.71, 25.34, 23.77, 18.43, 11.89, −5.71.

(*rel*)-(1′*R*,4′*S*)-9-[4-(Hydroxymethyl)-1,4-dimethylcyclopent-2-enyl]-adenine (14): To a solution of compound **11** (74.7 mg, 0.2 mmol) in THF (5 mL) at 0 °C, TBAF (0.3 mL, 1.0 M solution in THF) was added. The mixture was stirred at room temperature for 4 h, and concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1 : 6) to give compound **14** (35.7 mg, 69%) as a white solid: mp 178-180 °C; UV (H_2O) λ_{max} 262.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.52 (s, 1H), 8.20 (s, 1H), 5.58 (d, J = 5.2 Hz, 1H), 5.38 (d, J = 5.4 Hz, 1H), 4.82 (t, J = 5.0 Hz, 1H), 3.42-3.31 (dd, J = 12.0, 9.2 Hz, 2H), 2.46 (d, J = 12.2 Hz, 1H), 2.32 (d, J = 12.6 Hz, 1H), 1.76 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.66, 151.98, 150.12, 142.45, 138.35, 136.54, 119.61, 68.87, 61.72, 52.78, 47.77, 26.67, 23.67; Anal calc for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.35; H, 6.10; N, 26.82.

(*rel*)-(1′*R*,4′*S*)-1-[4-(Hydroxymethyl)-1,4-dimethylcyclopent-2-enyl]-thymine (15): Compound **15** was synthesized from compound **13** using the method described for synthesizing compound **14**: yield 65%; mp 168-170 °C; UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.15 (br s, 1H), 7.46 (s, 1H), 5.89 (d, J = 5.4 Hz, 1H), 5.64 (d, J = 5.2 Hz, 1H), 4.81(t, J = 5.2 Hz, 1H), 3.45 (dd, J = 11.8, 8.9 Hz, 2H), 2.50 (d, J = 12.4 Hz, 1H), 2.13 (d, J = 11.8 Hz, 1H), 1.41 (s, 3H), 1.24 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.52, 151.78, 139.12, 138.22, 136.24, 105.92, 68.23, 62.65, 52.76, 47.76, 26.73, 23.41, 11.88; Anal calc for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.47; H, 7.11; N, 11.02.

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